Supporting Material:

Evaluation of Other Arguments Against Testing Pesticides on Human Subjects

The Experiments Benefit Pesticide Companies

Opponents of pesticide testing on human subjects strongly object to experiments developed by pesticide companies because the experiments could benefit these companies by allowing pesticide users to avoid the higher safety levels required by the FQPA. If pesticide users must comply with the lower pesticide levels required by the FQPA, some pesticides may be ineffective. If some pesticides are ineffective, farmers will stop using them, which will have an adverse impact on pesticide producers. The companies sponsored human experiments in order to maintain something close to the status quo for allowable human pesticide exposures and to avoid losing business. According to the EWG (1998, p. 4), "pesticide manufacturers now have a powerful economic incentive to conduct human studies and submit them to the EPA when seeking regulatory approval for their products." According to Lynn Goldman, who headed the EPA's pesticide program for five years under the Clinton Administration, "for industry, there is an enormous amount of money in the balance…that's one of the troubling ethical issues (Goldman 2001, p. 1).

The fact that the pesticide industry stands to benefit from testing its products on human subjects is not argument against conducting this research. Pharmaceutical, biotechnology, and medical device companies generate billions of dollars in profits each year from products developed through research conducted on human subjects. Academic institutions and clinician-researchers also benefit financially from human experiments. The mere fact that someone may benefit economically from conducting research on human beings is not a good argument against that research, provided the research meets benefits society and meets ethical and legal requirements. Thus, we should not ask, "do

the studies benefit pesticide companies?," but we should ask "do the studies benefit society?" If the studies benefit companies but do not benefit society in any significant way, then the studies would be unethical (Emanuel et al 2000).

Even though the fact that the studies may benefit industry is not a good reason to reject the studies, it is ethically troubling, since the financial interests of the companies and their researchers could have an impact on the integrity of the research (Resnik 2001). There is a growing body of literature demonstrating that there is a significant funding effect in privately funded research: a very high percentage of industry-sponsored studies published in scientific journals demonstrate results that are favorable to the sponsor (Krimsky 2003, Angell 2004). There is also a body of literature demonstrating that researchers may bend or break human protections laws when they have financial interests in research, such as stock, patents, consulting agreements, or fees for recruiting patients (Krimsky 2003, Morin et al 2002).

The lesson that one can learn from this ethical concern about the studies is that companies, researchers, and universities must adhere to stringent standards for dealing with financial conflicts of interest. Many different agencies and organizations have developed policies for dealing with conflicts of interest in research, and most universities and journals have also adopted conflict of interest policies (Cho et al 2000; Association of American Medical Colleges 2002). There are different strategies for dealing with conflicts of interest, ranging from disclosure to prohibition to conflict management. In deciding which strategy is the most appropriate, one must consider a variety of factors, such as the benefits and risks of the conflict, as well as its potential biasing effect (Shamoo and Resnik 2003).

The Experiments are Underpowered

Critics of the disputed pesticide tests have argued that the tests were poorly designed because they did not use sample sizes large enough to detect statistically

significant effects. Some of the studies used fewer than fifteen subjects and one study used only six subjects (NRC 2004, EWG 1998). Statistical power is essential to ensuring that the study is scientifically and ethically sound (Halpern, Karlawish, and Berlin 2002). If a study is underpowered—if it does not have a large enough sample size to observe a statistically significant effect—then it will not produce scientifically valid results and it will unnecessarily expose human subjects to risks in research. Conversely, a study that is overpowered may produce scientifically valid results but may be ethically questionable because it may expose more subjects to research risks than is necessary to obtain significant results. The scientifically and ethically optimum sample size is one that is large enough to answer the questions that are posed but not unnecessarily large.

In the experiments we described earlier, the goal is to determine NOAEL for a pesticide. To determine this exposure level, researchers must discover the level that results in some observable, adverse effect. The size of the sample needed to observe the effect is inversely proportional to the size of the effect one attempts to observe: the smaller the sought after effect, the greater the sample size that is required. A sample size of 15 or fewer subjects may not be large enough to detect a statistically significant effect, if the effect is not very large. Experiments that are designed to detect a small effect, such as a small change in the level of a pesticide or biomarker in the bloodstream, will pose less of risk to subjects than experiments that are designed to detect a large effect, such as neurotoxicity. To protect subjects from harm, studies should be designed to detect small adverse effects, which can only be detected with larger sample sizes. IRBs should thoroughly review the statistical design of studies before allowing pesticide dosing experiments to take place (Oleskey et al 2004). To do this, IRBs may need to enlist the aid of scientists with the appropriate statistical expertise. The EPA should also provide some guidance to IRBs and researchers concerning these statistical issues.

The Slippery Slope

One might argue that testing pesticides on human subjects could establish a dangerous precedent and lead us to accept many human experiments that we would find to be ethically unacceptable. Pesticide experiments could erode our respect for human subjects and provide a justification for conducting other types of risky research not directly related to human health, such as testing cosmetics, pollutants, seatbelts, crash helmets, and bulletproof vests on human subjects. To avoid sliding down a slippery slope to the use of human subjects as guinea pigs in a wide variety of risky, non-medical experiments, society should prohibit the pesticide studies, according to this argument. The argument holds that even if the studies can be ethically designed, we should ban the studies because they could have adverse impacts on the ethics and regulation of human research.

Slippery slope arguments have been used to argue against in vitro fertilization, surrogate pregnancy, physician-assisted suicide, financial compensation to donors for organ transplantation, genetic testing, and many other controversial practices. A slippery slope argument is an inductive argument, in which one asserts that some adverse effect, E, is likely to occur after a series causes, C. The strength of a slippery slope argument depends on the strength of the inductive relationship between C and E (Walton 1992). If E is very likely, given C, then the argument is strong. A standard reply to a slippery slope argument is to assert that it is possible to break the connection between C and E by carefully regulating putatively ethical practices and drawing careful distinctions in ethics and the law (Resnik 1994, Schubert 2004). If these regulations are in place, then the adverse effect will be unlikely to occur. To prevent abuses of human subjects in research, one should carefully regulate and control pesticide experiments on human beings and draw careful distinctions between acceptable and unacceptable experiments. The report from the NRC (2004) is a step in this direction, since it discusses specific issues related to the regulation of pesticide experiments on human beings.

Supporting Material:

Scientific and Ethical Standards for Testing Pesticides on Human Subjects

We endorse the following scientific and ethical conditions for conducting pesticide experiments on human subjects (based on NRC 2004; Olesky et al 2004).

1. The knowledge gained from the study is expected to promote human health;
2. The knowledge cannot be obtained by other means, such as epidemiological or field studies, because the pesticide is not being used or not being used infrequently;
3. The study is not expected to cause serious or irreversible harm to the subjects.
4. Appropriate safeguards are in place to minimize harm to the subjects, such as the use of qualified medical and scientific personnel, exclusion of non-healthy subjects, careful monitoring of subjects during the experiments, adjustments of dosage regimens, reporting of adverse events, establishing independent DSMBs, and long-term follow-up of subjects.
5. The experiments must be scientifically well designed. The researchers should use appropriate methods to minimize bias and obtain statistically significant results. IRBs should pay careful attention to research design and questions concerning statistical power.
6. The results of all experiments must be publicly available within a reasonable time after the conclusion of such the experiments and submission of data to the EPA.
7. Informed consent should be obtained from research subjects under non-coercive conditions. Companies may not use their own employees. Subjects may be offered compensation for their time and inconvenience, but not so much money that the offer of money would constitute an undue influence on their decision-making. Subjects should be informed of the purposes of the research, study design, and benefits and risks of the experiments

8. Researchers should clearly articulate the benefits and the risks of the research, and the risks must be reasonable in relation to the benefits.
9. Selection of subjects should be equitable: researchers should not use race, ethnicity, gender, or socioeconomic status as a reason to qualify or disqualify subjects from a study.
10. Dosing studies of the effects of pesticides should never be conducted on vulnerable subjects, such as children, prisoners, and mentally disabled people, since these subjects cannot give valid consent for research participation. Only healthy adults should be allowed to participate in dosing studies, since these studies expose them to risks that are more than minimal without offering them medical benefits. The federal research regulations do not allow children or prisoners to participate in research than is more than minimal risk if the research does not benefit these subjects. However, it might be acceptable to enroll vulnerable subjects in field studies of the effects of pesticides, since these studies would not expose subjects to any risks over and above the risks they already face from pesticide exposure in their environment.
11. The confidentiality and privacy of subjects must be protected, according to appropriate ethical and legal standards.
12. Organizations that sponsor pesticide studies on human subjects should set aside funds to compensate subjects for research-related injuries.
13. IRBs should review the research according to the appropriate national or international standards, such as The Common Rule or the Helsinki Declaration. Researchers should report all adverse events to the IRB, to the research sponsors, and to other appropriate oversight bodies.

14. The EPA should establish an advisory board for pesticide experiments on human subjects. The board should develop guidance documents for IRBs and researchers.